IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

Shaun JORDAN et al.

Serial No.: 10/055,915 Group Art Unit: 1614

Filed: January 28, 2002 Examiner: Phyllis G. Spivack

For: 5-HT_{1A} RECEPTOR SUBTYPE AGONIST

D E C L A R A T I O N

Honorable Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

Tetsuro KIKUCHI, a Japanese citizen, residing at 157-13, Kawauchicho, Komatsunishi, Tokushima-shi, Tokushima, Japan, hereby solemnly and sincerely declares:

That I am one of the co-inventors of the above-identified application;

That I have read and understand the Official Action and the prior art references cited in the Official Action dated December 15, 2004;

That in order to demonstrate that the superior effect of the present compound for the treatment of depression, as comparing the comparative compound disclosed in the German counterparts (DE 2912105 C2 and

DE 2912105 C3) of the cited U. S. Patent No. 4,734,416 (Banno et al.), I conducted the following comparative pharmacological test:

Comparative Pharmacological Test:

1. Test compounds

Aripiprazole, 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril, was used as the compound of the present invention.

On the other hand, 7-{3-[4-(2,3-dichlorophenyl)-1-piperazinyl]propoxy}-3,4-dihydrocarbostyril, which is a compound within the scope of the disclosures of the cited U. S. Patent No. 4,734,416 and corresponds to the compound of Ex. No. 317 (DE 2912105 C2) and Ex. No. 311 (DE 2912105 C3) disclosed in the German counterparts of the cited U. S. Patent No. 4,734,416, was used as a comparative compound.

Hereinafter, the comparative compound is referred to as "Test compound 1".

2. Apparatus

Immobility time of the mice was measured using the animal movement analyzing system (SCANET system (MV-10 AQ, Toyo Sangyo Co. Ltd.). The system consisted of a square enclosure (56 x 56 cm) of which the side walls (20 cm height) was equipped with 144 pairs of

photosensors and was divided into 2 equal sections by two transparent plastic water tanks. Thus, two mice were tested simultaneously in this system. A non-transparent panel placed between the two tanks prevented the mice from seeing each other. Each pair of photosensors was scanned every 0.3 sec. to detect animal movement. The signals from photosensors reflected with the animal's movements were automatically imported into a personal computer (NEC, PC-9801). The behavioral data processing was performed on this personal computer.

3. Behavioral despair test

This experiment was conducted according to the methods described by Porsolt et al. (Porsort R.D., Anton G., Blavet N. and Jalfre M., Behavioral despair in rats: A new model sensitive to antidepressant treatments, Eur. J. Pharmacol., 1978; 47:379). Aripiprazole and Test compound 1 were administered orally (p.o.) for 2 hours respectively. Then, WAY-100635 (N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridimyl)-cyclohexanecarboxamide, referred to on page 18 of the present specification) was injected subcutaneously (s.c.), 30 min. before testing. All compounds were administered in a volume of 10 mL/kg for p.o. and 2 mL/kg for s.c. Each mouse was placed individually into Plexiglas cylinders, equipped with the SCANET (height,

30cm; diameter, 9cm) containing 9.5 cm of water maintained at 23-24°C and immobility time was recorded during 6 min. test. Data analysis was performed using the immobility time in whole 6 min. test period.

4. Statistical analysis

The difference of immobility time between vehicle alone-group and WAY-100635 alone-group was evaluated by two-tailed t-test. The differences of immobility time between WAY-100635 alone-group and combination of each test drug with WAY-100635 group were assessed by two-tailed Dunnett's test.

Results were considered as significant for values of $p < 0.05$. All statistical analyses were performed using SAS, release 8.1.

5. Results (Combination studies of test compounds with WAY-100635)

The effects of each drug on immobility time prolonged by WAY-100635 were investigated. A subcutaneous dose of 10 mg/kg WAY-100635 significantly increased immobility time in forced swimming test and the dose was therefore used in all combination studies. The results are shown in the Table below. Aripiprazole at a dose of 10 mg/kg p.o. significantly decreased prolongation of the immobility time by WAY-100635.

Test compound 1 did not alter the WAY-100635-induced prolongation of immobility time.

Table

Effects of each agent on immobility time in forced swimming test in combination with WAY-100635 10 mg/kg s.c.

Treatment 1	Dose (mg/kg p.o.)	Treatment 2	Dose (mg/kg s.c.)	Immobility time Mean ± S.E (sec)
Vehicle	0	Vehicle	0	209.5 ± 12.8
		WAY100635	10	248.4 ± 5.7#
Aripiprazole	3			232.0 ± 11.6
	10			216.0 ± 9.0*

Mean ± S.E., n=10. #P<0.05 vs. vehicle + vehicle group (two-tailed t-test)
*P<0.05 vs. vehicle + WAY100635 group (two- tailed Dunnett's test at each compound in comparison of 3 groups)

Treatment 1	Dose (mg/kg p.o.)	Treatment 2	Dose (mg/kg s.c.)	Immobility time Mean ± S.E (sec)
Vehicle	0	Vehicle	0	201.5 ± 9.9
		WAY100635	10	225.9 ± 5.0#
Test compound 1	3			213.7 ± 7.6[NS1]
	10			219.9 ± 17.1[NS1]

Mean ± S.E., n=7-8. #P<0.05 vs. vehicle + vehicle group (two-tailed t-test)
[NS1]NOT significant vs. vehicle + WAY100635 group (two- tailed Dunnett's test).

Aripiprazole at a dose of 10 mg/kg, p.o. significantly shortened the prolonged immobility time induced by WAY-100635. These findings suggest that aripiprazole may have an improvement effect on animal model of depression induced by the reduction of serotonergic neurotransmission mediated by at least 5-HT_{1A} receptors. On the other hand, Test compound 1 may not have an improvement effect on animal model of depression induced by the reduction of serotonergic neurotransmission mediated by at least 5-HT_{1A} receptors.

The undersigned declarant declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 30th day of May, 2005.

Tetsuro Kikuchi

Tetsuro KIKUCHI